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REVIEW ARTICLE

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Dual impact from coincide potential complications of cancer therapy and sarcopenia: a narrative review

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ABSTRACT

Sarcopenia is a disorder of progressive loss of skeletal muscle mass and strength that is linked with multiple complications, decreased physical activity, lower quality of life and accelerated mortality rate. It is more common among cancer patients and identified with reduced tolerance by the toxic effects from cancer therapy, negative outcomes, lowered response and overall survival rate. This narrative review aims to demonstrate the dual impact from the co-occurrence of cancer therapy; chemotherapy, radiotherapy, immunotherapy, and sarcopenia alongside the potential complications from their coincide effects on cancer prognosis. By searching through data sets, all articles that focused on sarcopenia and cancer therapy were collected in the indexed journals between the years 2000 and 2021 that could provide findings for the potential complications from the coinciding effects of cancer therapy and sarcopenia in cancer patients receiving chemo-radio- and immunotherapy. Outcome measures were the rate of studies showing potential complications from the co-occurrence of cancer therapies and sarcopenia. A total of hundred-two cohort studies were enrolled. The majority were about chemotherapy and sarcopenia (45%). About 56.9 % of the studies designed as retrospective analysis, and a high proportion were about chemotherapy and sarcopenia (21.6%). About 63.7% of the studies reported skeletal muscle index as the primary marker. Lower than half of the reviewed studies revealed a significant increase in the rate of sarcopenia (47%). The direct toxic effects of chemotherapy on skeletal muscle were reported in 13.7% of the studies. Studies that reported the impact of sarcopenia on a reduction in chemotherapy cycles were about 10.8%. About 11.8% and 14.7% of the studies showed lowered overall survival by the coinciding impact of chemotherapy/radiotherapy and sarcopenia, respectively. In conclusion, the evaluation of sarcopenia in cancer patients should be considered a primary part of oncological care in cancer patients as there are potential complications and poor survival from the co-occurrence of sarcopenia and different cancer therapies.

Key words: cancer, chemotherapy, immunotherapy, radiotherapy, skeletal muscle, sarcopenia

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Introduction

Sarcopenia term first took its place in medical literature in the late 1980s by Rosenberg and consists of two words: “sarx (muscle)” and “penia (loss)”. It is defined as a progressive generalized loss of muscle mass and strength as a secondary complication to chronic disease conditions, sedentary lifestyle, and malnutrition [1–3]. Sarcopenia is strictly correlated with increased risk of functional impairment, disability, physical insufficiency, falls and fractures, low quality of life, poor patient outcomes, and a high rate of mortality [3]. It is categorised into three stages based on the definition of the European Working Group on Sarcopenia in Older People (EWGSOP). A pre-sarcopenia stage is characterized by a decrease in muscle mass. This stage does

not affect muscle strength and physical performance and can be identified by accurate measuring of muscle mass. A sarcopenia phase is manifested by a decrease in muscle mass, strength, or physical performance. In severe sarcopenia, there is an obvious decrease in muscle mass, strength, and physical performance [4, 5].

In sarcopenia, potential components for loss of muscle quality, mass, and strength include a diminished skeletal muscle innervation and capillary density and the specific decay of type II muscle filaments; that is, a decrease in the motor units involved in the binding of neurons and muscle fibres [6]. The immediate result of sarcopenia is the loss of skeletal muscles, which are not just an essential piece of the motor system but also, modulate immune and inflammatory processes by secreting multiple cytokines, such as tissue necrosis factor-α (TNF) to promote systemic inflammation. Along these lines, sarcopenia may bring down natural killer (NK) cells in cancer patients, thereby debilitating the anti-tumour immune response and worsening patient prognosis [7–9]. Myokines, like interleukin (IL)-6, can have anti-tumorigenic impacts by interacting with NK cells and actuating the production of IL-1 receptor antagonist and IL-10 by the molecules with anti-inflammatory effects [10, 11]. On the other hand, the pro-inflammatory factors delivered by both immune cells and tumour cells advance muscle tissue disintegration and restrain skeletal muscle cell differentiation which can inhibit protein synthesis and muscle regeneration, ultimately prompting muscle atrophy [12]. Besides, TNF-α can straightforwardly instigate muscle atrophy through the ubiquitin-proteasome system (UPS) [13].

Furthermore, many risk factors are associated with the development of sarcopenia. They include age-related changes in tissue secretion or responsiveness to trophic hormonal factors, nutritional insufficiency, a diet poor in protein, muscle fibre count, genetic factors, immobility, post-traumatic, smoking, alcohol, sedentary lifestyle and acute and chronic co-morbid disease conditions such as obesity, osteoporosis and type 2 diabetes mellitus, insulin resistance and underlying malignancy [14, 15].

This narrative review aims to demonstrate the bimodal impact from the co-occurrence of cancer therapy; chemotherapy, radiotherapy, immunotherapy, and sarcopenia alongside the potential complications from their coincide effects on cancer prognosis.

Methods

Search and data extraction

By searching through data sets within PubMed, Google Scholar, ISI, Scopus, and Embase, all articles that focused on sarcopenia and cancer therapy were gathered in the indexed journals between the years 2000 and 2021 that could provide information on the correlated effects of different therapeutic agents used in cancer therapy and sarcopenia. The search strategy for this study was performed utilizing the terms of medical subject headings (MeSH) and combinations of the keywords according to the following: sarcopenia, cancer, chemotherapy, radiotherapy, chemo-radiotherapy, immunotherapy, immune checkpoint inhibitors, skeletal muscle, and body mass index. Inclusion criteria were all articles that focused on the co-existence of cancer therapy and sarcopenia regarding the potential impact of cancer therapy (chemo-radio-and immunotherapy)-induced toxicity on the incidence and prognosis of sarcopenia and vice versa. These included randomised clinical trials, case-control, and retrospective studies; while the titles, abstracts, and full texts of all imported studies were screened by the researchers. Data were extracted from included studies for the following evidence: author, country, year of publication, type of study, sample size, cancer type, cancer therapy, duration of therapy in days, body composition marker, rate of sarcopenia evaluation, and summary of main outcomes. The accuracy and quality of the included data were additionally checked and the review process excluded irrelevant studies and articles, and those not in the English language (Fig. 1).

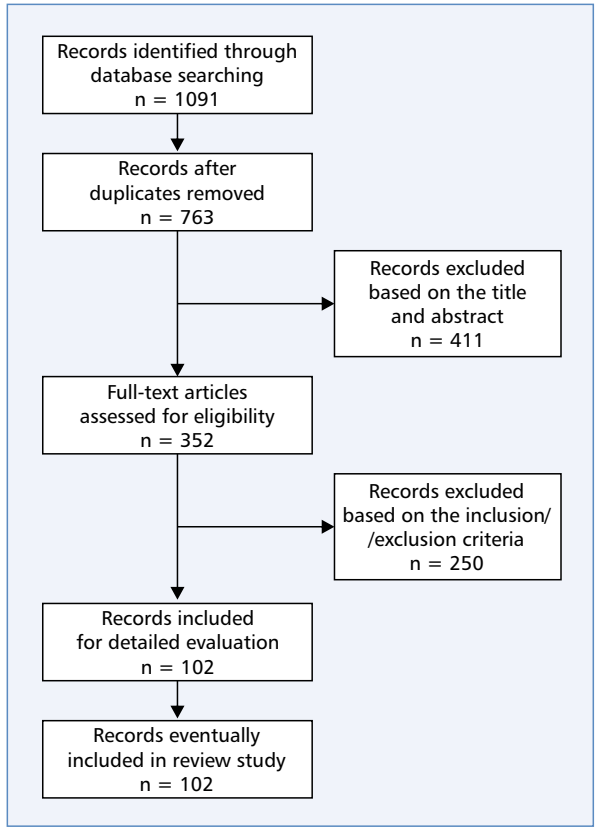

Figure 1. Flowchart for the database searching and articles selection

Results

A review of hundred-two cohort studies conducted on the potential complications from coinciding effects of cancer therapy and sarcopenia in cancer patients receiving chemo-radio- and immunotherapy revealed varied results. Most of the reviewed studies were about the potential impact of cancer chemotherapy and sarcopenia (45%) (Tab. 1 and 2); while an equal proportion of the reviewed studies was about the impact of sarcopenia in chemo-radiotherapy and immunotherapy (27.5%), as shown in Tables 1, 3 and 4.

The present study showed that a total of 58 studies (56.9%) were designed as retrospective analyses, and a high proportion of these retrospective studies was about cancer chemotherapy and sarcopenia (n = 22) (Tab. 1 and 2). Nearly an equal proportion of the reviewed studies were conducted among patients who suffered from oesophagogastric carcinoma received chemotherapy and non-small cell lung cancer patients received immunotherapy (NSCLC) (13.7%, 14.7%), respectively (Tab. 1, 3 and 4). Furthermore, platinum-based compounds represented the most common chemotherapeutic agents administered within the scope of chemotherapy and sarcopenia (13.7%) (Tab. 1 and 2); while both pembrolizumab and nivolumab represented the most common immune checkpoint inhibitors (15.7%) administered within the scope of immunotherapy and sarcopenia, as shown in Tables 1, 3 and 4.

Regarding the marker of body composition (a surrogate for skeletal muscle mass), skeletal muscle index

Table 1. Summary of findings for the reviewed cohort studies

Variable	Number of Reviewed Studies (n = 102)	Percentage
Studies-related cancer therapy		
Chemotherapy	46	45.0
Chemo-radiotherapy	28	27.5
Immunotherapy	28	27.5
Study design		
Retrospective	58	56.9
Prospective	44	43.1
Cancer diagnosis		
Oesophagogastric carcinoma	14	13.7
Non-small cell lung carcinoma (NSCLC)	15	14.7
Anticancer therapy		
Platinum-based compounds	14	13.7
Pembrolizumab	16	15.7
Nivolumab	16	15.7
Surrogate for skeletal muscle mass		
Skeletal muscle index (Total)	65	63.7
Skeletal muscle index (chemotherapy)	29	44.6
Skeletal muscle index (chemo-radiotherapy)	18	27.7
Skeletal muscle index (immunotherapy)	18	27.7
Rate of sarcopenia	48	47
Impact of chemotherapy on sarcopenia incidence	14	13.7
Impact of sarcopenia on administration of chemotherapy schedules	11	10.8
Lowered overall survival by coincide impact of chemotherapy and sarcopenia	12	11.8
Lowered overall survival by coincide impact of radiotherapy and sarcopenia	15	14.7
Impact of sarcopenia on administration of immunotherapy schedules	8	7.8
Overall Outcome*	95	93.1

Data presented as number (n) and percentage (%); *A significant negative impact to the co-existence of sarcopenia and cancer therapy

Table 2. Summary of clinical cohort studies regarding the potential impact of cancer chemotherapy and sarcopenia

Author/Country/ /Year	Study Design	Sample Size	Cancer Type	Chemo-therapy	Duration (pre-post therapy in Days)	Body Composit-ion Marker	Rate of Sarcopenia Evaluation		Main Outcomes	Ref.
							Baseline Sarcopenia (%)	Post-therapy sarcopenia (%)		
Gastrointestinal										
Awad et al./UK/2012	Observational study	47	Oe-sopha-gogas-tric	Epirubicin/ Cisplatin/5-fluorouracil	107	Fat mass, Fat free mass	57	79	Neoadjuvant chemothera-py was associated with an increase of sarcopenia	[32]
Yip et al./UK/2014	Prospective study	35	Oesophag-eal	Multiple chemotherapy regimens	60	Fat mass, Fat free mass, subcutan-eous fat to muscle ratio	26	43	Sarcopenia increased following neoadjuvant chemotherapy	[33]
Reisinger et al./ Neth-erlands/2015	Prospective study	114	Oesophag-eal	Multiple chemotherapy regimens	111	Skeletal muscle loss index	56	67	Measurement of muscle mass loss provide assess-ment to identify unfavora-ble postoperative outcome	[121]
Liu et al./Japan/2016	NA	84	Oesophag-eal	5-fluorouracil, cisplatin or nedaplatin	56	Psoas muscle index	NA	NA	Decreased psoas muscle index correlates well with a poor prognosis	[21]
Elliott et al./ Ire-land/2017	Prospective study	252	Oesophag-eal	(Cisplatin/5-Fluorouracil); Carboplatin/Paclitaxel); (Etoposide, Cisplatin, Fluorouracil/Capecit-abine)	365	Lean body mass, skeletal muscle in-dex, fat mass	16	31	Sarcopenia is associated with an increased risk of major postoperative com-plications	[122]
Paireder et al./ Aus-tria/2018	Retrospective study	130	Oesophag-eal	Taxane/platinum taxane+platinum	NA	Skeletal muscle index	42.3	57.7	Sarcopenia impacts long-term outcome	[23]
Daly et al./ Ire-land/2018	Prospective obser-vational study	225	Foregut	Multiple chemotherapy regimens	118	Skeletal muscle index, adipose tis-sue area	40	NA	Patients experience signifi-cant losses of muscle dur-ing chemotherapy	[34]
Guinan et al./ Ire-land/2018	Prospective obser-vational study	28	Oesophag-eal	(Etoposide, Cisplatin, Fluorouracil/ Capecit-abine); (Cisplatin/5-Fluo-rouracil, Carboplatin/Pa-clitaxel)	96	Lean body mass	7	22	Participants experience de-clines in muscle mass and strength	[35]

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Table 2 cont. Summary of clinical cohort studies regarding the potential impact of cancer chemotherapy and sarcopenia

Author/Country/ /Year	Study Design	Sample Size	Cancer Type	Chemo-therapy	Duration (pre-post therapy in Days)	Body Composit-ion Marker	Rate of Sarcopenia Evaluation		Main Outcomes	Ref.
							Baseline Sarcopenia (%)	Post-therapy sarcopenia (%)		
Järvinen et al. / Finland/2018	Retrospective cohort study	118 (115)	Oesophag-eal	epirubicin–oxaliplatin–capecitabine	33	Skeletal muscle index	80	80	Loss of skeletal muscle tissue correlates with worse overall survival	[24]
Dijksterhuis et al./ Netherlands/2019	NA	88	Oesopha-gogastric	Capecitabine/oxaliplatin	79	Skeletal muscle index, reflecting muscle mass, and skeletal muscle density	49	55	Sarcopenia was not associated with survival or treatment-related toxicity	[123]
Ma et al./South Korea/2019	Retrospective study	198	Oesophag-eal cancer	Chemo-radiotherapy (multiple chemotherapy regimens)	NA	Skeletal muscle index	NA	NA	Sarcopenia can be a useful predictor for long-term prognosis	[22]
Ota et al./Japan/2019	Retrospective study	31	Oesoph- ageal cancer	Cisplatin, 5-fluorouracil/ cisplatin, 5-FU, and docetaxe	NA	Skeletal muscle index	51.6	NA	Potential utility of sarcopenia assessment	[124]
Voisinet et al./ France/2020	Retrospective study	46	Oesog- astric adenocar- cinoma	NA	180	Psoas, paraspinal, abdominal wall muscles	6.7	60	Feeding jejunostomy with enteral nutritional seemed to efficiently counteract sarcopenia occurrence	[125]
Palmela et al./ Portugal/2017	Retrospective study	48	Gastric	Multiple chemotherapy regimens	86	Skeletal muscle index, visceral fat index	23	58	Sarcopenia associated with early termination of neoadjuvant chemotherapy	[55]
Dalal et al./USA/2012	Prospective cohort study	41	Pancreatic	Bevacizumab, capecitabine	104	Skeletal muscle, visceral adipose tissue, subcutan- eous adipose tissue	63	90	Obese patients experience higher losses in weight	[126]
Fogelman et al./ USA/2014	Prospective study	53	Pancreatic	Gemcitabine, erlotinib, MK-0646	60	Skeletal muscle index	NA	NA	Metastatic pancreatic cancer patients can be expected to lose muscle mass	[127]
Choi et al./South Korea/2015	Retrospective study	484	Pancrea-tic cancer	Multiple chemotherapy regimens (Gemcitabine, FOLFIRINOX)	NA	Skeletal muscle index	21	53	Sarcopenia was poor prognostic factors in advanced pancreatic cancer	[25]

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Table 2 cont. Summary of clinical cohort studies regarding the potential impact of cancer chemotherapy and sarcopenia

Author/Country/ /Year	Study Design	Sample Size	Cancer Type	Chemo-therapy	Duration (pre-post therapy in Days)	Body Composit-ion Marker	Rate of Sarcopenia Evaluation		Main Outcomes	Ref.
							Baseline Sarcopenia (%)	Post-therapy sarcopenia (%)		
Cooper et al./ USA/2015	Prospective study	89	Pancreatic	Gemcitabine, cisplatin	135	Skeletal muscle, adipose tissue com-partments	52	59	Further depletion of skele-tal muscle occurred during neoadjuvant therapy	[36]
Benjamin et al./ USA/2018	Retrospective study	24	Pancreatic	Multiple chemotherapy regimens	NA	Total psoas area index	38	NA	A significant decrease in total psoas area index dur-ing treatment with received neoadjuvant chemotherapy	[37]
Sandini et al./Ita-ly/2018	Retrospective co-hort study	193	Pancreatic	Multiple chemotherapy regimens	180	Total adipose tis-sue area, visceral adipose tissue area, skeletal lean mass	43	41	Patients experience a sig-nificant loss of adipose tissue during neoadjuvant chemotherapy	[38]
Prado et al./Cana-da/2007	Prospective study	62	Colon cancer	5-fluorouracil, leuco-vorin	168	Lean body mass	NA	NA	Lean body mass is a signifi-cant predictor of toxicity	[56]
Poterucha et al./ USA/2012	NA	57	Colorectal cancer	Multiple chemotherapy regimens, bevacizumab	90	Skeletal muscle index	NA	NA	Prescribed bevacizumab appear to lose weight and muscle in the absence of cancer progression	[39]
Barret et al./ France/2014	Prospective, cross-sectional, multicenter study	51	Colorectal cancer	Fluoropyrimidine ± oxaliplatin, irinotecan	60	Areas of muscle tissue, visceral adipose tissue, sub-cutaneous adipose tissue	NA	70.6	Sarcopenia significantly associated with severe chemotherapy toxicity	[57]
Jung et al./ South Korea/2015	Prospective study	229	Colon cancer	Oxaliplatin, 5-fluoroura-cil, leucovorin	180	Psoas muscle index	NA	NA	Decreased muscle mass was associated with increased risk of grade 3-4 toxicity and poor prog-nosis	[26]
Miyamoto et al./Ja-pan/2015	Retrospective study	182	Unresect-able colorectal cancer	Oxaliplatin, irinotecan	70	Skeletal muscle index	73	NA	Skeletal muscle loss was an independent, negative prognostic factor	[27]

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Table 2 cont. Summary of clinical cohort studies regarding the potential impact of cancer chemotherapy and sarcopenia

Author/Country/ /Year	Study Design	Sample Size	Cancer Type	Chemo-therapy	Duration (pre-post therapy in Days)	Body Composit-ion Marker	Rate of Sarcopenia Evaluation		Main Outcomes	Ref.
							Baseline Sarcopenia (%)	Post-therapy sarcopenia (%)		
Ali et al./France, Canada/2016	Prospective randomized clinical trials	138	Colon cancer	FOLFOX (Folinic acid, 5FU, oxaliplatin, irinotecan ± cetuximab)	180	Lean body mass	NA	NA	Low lean body mass is a significant predictor of toxicity	[54]
Blauwhoff-Buskermolen et al./ Netherlands/2016	Prospective study	63	Colorectal cancer	Multiple chemotherapy regimens	NA	Skeletal muscle index	57	70	Muscle area decreased significantly during chemotherapy and was independently associated with survival	[20]
Eriksson et al./Sweden/2017	Retrospective study	225	Resectable colorectal liver metastases	Multiple chemotherapy regimens (majorly oxaliplatin-based)	960	Skeletal muscle index	NA	61	Skeletal muscle mass decreases during neoadjuvant chemotherapy and impairs the conditions for adjuvant chemotherapy	[40]
Antoun et al./ France/2019	Prospective multicenter, randomized, open-labelled, non-comparative phase II trial	76	Colorectal cancer	Multiple chemotherapy regimens	120	Skeletal muscle index	NA	NA	Skeletal muscle mass depletion was not associated with survival or chemotherapy toxicity	[128]
Derksen et al./ Netherlands/2019	Randomized controlled phase III trial	300	Colorectal cancer	Multiple chemotherapy regimens	126	Skeletal muscle index	NA	NA	Skeletal muscle index loss was associated with lifestyle-related as well as tumour- and treatment-related factors	[28]
Kurk et al./ Netherlands/2019	Observation trial study	414	Colorectal cancer	Capecitabine, bevacizumab, oxaliplatin	NA	Skeletal muscle index, body mass index	54, 46	NA	Sarcopenia and/or muscle loss was associated with an increased risk of dose-limiting toxicities	[58]
Kobayashi et al./Japan/2018	Retrospective study	102	Hepatocell-ular carcinoma	Transcatheter arterial chemoembolization and transcatheter arterial infusion multiple chemotherapy	180	Skeletal muscle index	NA	NA	Rate of change in skeletal muscle mass was an independent prognostic factor	[129]

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Table 2 cont. Summary of clinical cohort studies regarding the potential impact of cancer chemotherapy and sarcopenia

Author/Country/ /Year	Study Design	Sample Size	Cancer Type	Chemo-therapy	Duration (pre-post therapy in Days)	Body Composit-ion Marker	Rate of Sarcopenia Evaluation		Main Outcomes	Ref.
							Baseline Sarcopenia (%)	Post-therapy sarcopenia (%)		
Lung										
Stene et al./Norway/2015	Pilot observation-al cohort study	35	Non-small cell lung carcino-ma cancer (NSCLC)	Carboplatin Vinorelbine Gemcitabine	88	Skeletal muscle index	NA	NA	Almost half of the patients had stable or increased muscle mass during chem-otherapy	[21]
Go et al./Korea/2016	Retrospective study	117	SCLC	Chemotherapy (Etopo-side, platinum /Iri-notecan, cisplatin) or chemo-radiotherapy	NA	Skeletal muscle index	24.8	NA	Baseline sarcopenia is asso-ciated with poor prognosis and a high incidence of dose-limiting toxicity of the standard first-line treat-ment	[29]
Atlan et al./ France/2017	Retrospective study	64	NSCLC	NA	133	Skeletal muscle index, total adipose tissue	49	48.1	Skeletal muscle mass is wasting is lower when initial skeletal muscle mass and BMI values are low	[130]
Nattenmüller et al./ Germany/2017	Retrospective sin-gle centre study	200	NSCLC	Multiple chemotherapy regimens	125	Visceral, subcuta-neous-fat-area, in-ter-muscular-fat-ar-ea, muscle-density, muscle-area, skele-tal-muscle index	NA	NA	After chemotherapy, pa-tients exhibited sarcopenia with decreased muscle	[41]
Goncalves et al./ USA/2018	Retrospective study	88	NSCLC	Taxane, gemcitabine, bevacizumab	120	Skeletal muscle 2-[18F]-fluoro-2-de-oxy-d-glucose	NA	NA	During chemotherapy skeletal muscle volume and metabolism are altered	[42]
Kakinuma et al./Ja-pan/2018	Retrospective study	44	NSCLC	Not-specified (Po-ly-chemotherapy)	152	Skeletal muscle index	NA	NA	Skeletal muscle loss was higher in patients receiving cytotoxic chemotherapy	[131]
Breast and Ovarian										
Prado et al./Cana-da/2009	Prospective Study	55	Breast cancer	Capecitabine	30	Skeletal muscle index	25	50	Sarcopenia is a significant predictor of toxicity and tumour progression	[30]

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Table 2 cont. Summary of clinical cohort studies regarding the potential impact of cancer chemotherapy and sarcopenia

Author/Country/ /Year	Study Design	Sample Size	Cancer Type	Chemo-therapy	Duration (pre-post therapy in Days)	Body Composit-ion Marker	Rate of Sarcopenia Evaluation		Main Outcomes	Ref.
							Baseline Sarcopenia (%)	Post-therapy sarcopenia (%)		
Prado et al./Canada/2011	Prospective study	132	Breast cancer	5FU, epirubicin, cyclophosph-amide	180	Lean body mass	NA	NA	Lean body mass was lower for patients presenting with toxicity	[59]
Mazzuca et al./ Italy/2018	Retrospective study	21	Breast cancer	Anthracycline-based chemotherapy	NA	Skeletal muscle index	38	48	Lean body mass loss is associated with higher grade of toxicity	[60]
Rier et al./ Netherlands/2018	Single-centre, retrospective study	98	Metastatic breast cancer	5-fluorouracil, doxorubicin, cyclophosphamide/ Paclitaxel	118	Lumbar skeletal muscle index	NA	NA	Muscle attenuation decreased during treatment	[62]
Rutten et al./ Netherlands/2016	Retrospective study	123	Ovarian cancer	Multiple chemotherapy regimens	84	Surface areas of skeletal muscle	NA	NA	Patients with ovarian cancer have a worse survival when they lose skeletal muscle	[31]
Bladder										
Zargar et al./ USA/2017	Retrospective study	60	Bladder cancer	Multiple chemotherapy regimens (majorly gemcitabine-cisplatin)	126	Bilateral total psoas muscle volume	NA	NA	A decline in psoas muscle volume during neoadjuvant chemotherapy and associated with the need for dose reduction/dose delay	[43]
Rimar et al./ USA/2018	Retrospective study	26	Bladder carcinoma	Methotrexate, vinblastine, doxorubicin, cisplatin/ gemcitabine, cisplatin/ gemcitabine, carboplatin	110	Lumbar skeletal muscle index, visceral adipose index, subcutaneous, intramuscular adipose index	69	81	A significant decrease in lean muscle mass with an associated increase in the prevalence of sarcopenia	[44]
Others										
Xiao et al./USA/2016	Retrospective cohort study	191	Diffuse large B-cell lymphoma	Cyclophos-phamide, doxorubicin, vincristine/ prednisone, ± rituximab	90	Muscle, subcutaneous fat, visceral fat areas	NA	NA	Survivors undergo unfavorable long-term body composition changes	[132]

NA — non-available

Table 3. Summary of clinical cohort studies regarding the potential impact of radiotherapy/chemo-radiotherapy and sarcopenia

Author/ /Country/Year	Study Design	Sample Size	Cancer Type	Radiotherapy or Chemo-radiotherapy	Duration (pre-post therapy in days)	Body Composition Marker	Rate of Sarcopenia Evaluation		Main Outcomes	Ref.
							Baseline Sarcopenia (%)	Post-therapy sarcopenia (%)		
Head and neck carcinoma (HNC)										
Grossberg et al./ USA/2016	Retrospective study	2840	HNC	Radiotherapy	2058	Skeletal muscle index	35.3	65.8	Diminished skeletal muscle mass	[133]
Cho et al./ South Korea/2018	Retrospective study	221	HNC	Chemo-radiotherapy	NA	Skeletal muscle index	NA	48	Sarcopenia is associated with significantly inferior overall survival, progression-free survival and RT interruption more frequently	[80]
Ganju et al./ USA/2019	Retrospective study	246	HNC	Chemo-radiotherapy (cisplatin, cetuximab),	1053	Lumbar skeletal muscle index	NA	58.1	Sarcopenic patients are more likely to require radiation treatment breaks and suffer chemotherapy toxicity	[73]
van Rijn-Dekker et al./ Netherlands/2020	Prospective study	750	HNC	Chemo-radiotherapy (cisplatin, carboplatin/5-FU or cetuximab)	720	Skeletal muscle index	NA	NA	Sarcopenia is an independent prognostic factor for worse survival outcomes and is associated with physician-rated toxicity	[82]
Chauhan et al./India/2020	Short-term, longitudinal cohort study	19	HNC	Chemo-radiotherapy	49	Skeletal muscle index	31.5	89.4	Patients showed clinically significant increases in the incidence of sarcopenia	[134]
Thureau et al./ France/2020	Observational prospective, unicentric study	243	HNC	Chemo-radiotherapy (Cisplatin, cetuximab)	NA	Skeletal muscle index	NA	41.7	Pretherapeutic sarcopenia remains frequent and predicts overall survival and disease-free survival	[83]
Respiratory										
Op den Kamp et al./ Netherlands/ 2014	Retrospective cohort study	203	Non-small cell lung carcinoma (NSCLC)	Chemo-radiotherapy	NA	Limb muscle strength	NA	NA	Weight loss starts early and requiring timely and intense nutritional rehabilitation	[135]
Sanders et al./ Netherlands/2016	Retrospective study	287	Non-small cell lung carcinoma (NSCLC)	Chemo-radiotherapy (majorly platinum-based chemotherapy + etoposide)	NA	Early weight loss	NA	NA	Early weight was found to be associated with worse prognosis	[84]
Kiss et al./Australia/2019	Prospective study	41	Non-small cell lung carcinoma (NSCLC)	Multiple chemotherapy regimens	150	Muscle area, muscle density	61	85	Significant loss of muscle area and muscle density occurs early during therapy	[136]

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Table 3 cont. Summary of clinical cohort studies regarding the potential impact of radiotherapy/chemo-radiotherapy and sarcopenia

Author/ /Country/Year	Study Design	Sample Size	Cancer Type	Radiotherapy or Chemo-radiotherapy	Duration (pre-post therapy in days)	Body Composition Marker	Rate of Sarcopenia Evaluation		Main Outcomes	Ref.
							Baseline Sarcopenia (%)	Post-therapy sarcopenia (%)		
Shen et al./China/2013	Retrospective cohort study	2433	Nasopharyngeal carcinoma (NPC)	Radiotherapy	60-3750	High weight loss, low weight loss	NA	NA	High weight loss was independently associated with poor survival in NPC	[85]
Li et al./China/2017	Retrospective study	322	Nasopharyngeal carcinoma	Radiotherapy	2190	Body weight loss	NA	93.5	Acute radiation toxicities had significant and independent impact on weight loss	[75]
Gastrointestinal										
Olson et al./Portland/2020	Retrospective study	245	Oropharyngeal squamous cell carcinoma	Radiotherapy	NA	Third lumbar skeletal muscle index	NA	55.1	Sarcopenia has a negative association with survival for patients	[86]
Murimwa et al./ USA/2017	Retrospective study	56	Oesophageal cancer	Chemo-radiotherapy	NA	First full slice of the L4 vertebra, psoas muscle	NA	NA	Sarcopenia was associated with a significant increase in acute grade ≥3 toxicity	[137]
Panje et al./ Switzerland/2019	Prospective Study	61	Oesophageal cancer	Chemo-radiotherapy (multiple chemotherapy regimens)	90	Skeletal muscle index	29.5	63.9	Neoadjuvant chemoradiation increased the percentage of sarcopenia. Sarcopenic patients are at higher risk for increased toxicity during therapy	[76]
Ma et al./ South Korea/2019	Retrospective study	287	Oesophageal cancer	Chemo-radiotherapy	90-180	Skeletal muscle index	NA	8.7	Sarcopenia can be a useful predictor for long-term prognosis	[87]
Yoon et al./Korea/2020	Retrospective study	248	Oesophageal cancer	Chemo-radiotherapy (5-fluorouracil, cisplatin)	35	Skeletal muscle index	62.9	83.5	Excessive muscle loss was a significant prognostic factor for overall survival and recurrence free survival	[88]
Mallet et al./ France/2020	Retrospective study	97	Oesophageal cancer	Chemo-radiotherapy	NA	Skeletal muscle index	56	93	Sarcopenia is a powerful independent prognostic factor, associated with a rise of the overall mortality	[81]
Liang et al./China/2021	Retrospective study	100	Oesophageal cancer	Radiotherapy	360	Skeletal muscle index	NA	70.1	Sarcopenia can independently predict the survival of patients	[89]
Shiba et al./Japan/2018	Retrospective study	68	Hepatocellular carcinoma (HCC)	Radiotherapy	1005	Skeletal muscle index	NA	32.4	Sarcopenia was not a prognostic factor for patients with HCC treated with C-ion RT	[138]
Lee et al./South Korea/2019	Retrospective study	156	Hepatic-cellular carcinoma (HCC)	Radiotherapy	279	Skeletal muscle index	63.5	NA	Sarcopenia, was associated with poor survival	[90]

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Table 3 cont. Summary of clinical cohort studies regarding the potential impact of radiotherapy/chemo-radiotherapy and sarcopenia

Author/ /Country/Year	Study Design	Sample Size	Cancer Type	Radiotherapy or Chemo-radiotherapy	Duration (pre-post therapy in days)	Body Composition Marker	Rate of Sarcopenia Evaluation		Main Outcomes	Ref.
							Baseline Sarcopenia (%)	Post-therapy sarcopenia (%)		
Lin et al./China/2016	Retrospective study	364	Rectal cancer	Chemo-radiotherapy (oxaliplatin, capecitabine/ oxaliplatin, leucovorin, 5-FU)	NA	Body mass index	66.2	100	Severe weight loss compromises survival outcome	[91]
Park et al./ South/2018 Korea	Retrospective study	104	Rectal cancer	Chemo-radiotherapy (5FU, capecitabin)	NA	Skeletal muscle index	36.7	40	Sarcopenia is a poor prognostic factor in older patients	[92]
Cervical										
Kiyotoki et al./Japan/2018	Retrospective study	60	Cervical cancer	Chemo-radiotherapy (cisplatin, nedaplatin/ ifosfamide + nedaplatin)	1005	Skeletal muscle, iliopsoas muscle	NA	NA	Sarcopenia was revealed to be an important prognostic factor	[93]
Matsuoka et al./ Japan/2019	Retrospective study	236	Cervical cancer	Chemo-radiotherapy (cisplatin, nedaplatin/ ifosfamide + nedaplatin)	30-4950	Psoas muscle index, skeletal muscle index	NA	NA	Sarcopenia is not a predictive factor of outcome	[139]
Others										
Couderc et al./ France/2020	Prospective study	31	Prostate cancer	Androgen deprivation therapy+ radiotherapy	NA	Appendicular skeletal muscle mass	25.8	NA	A high prevalence of muscle disorders	[140]
Pielkenrood et al./ Netherlands/2020	Prospective cohort study	310	Spinal metastases	Radiotherapy	202	Visceral fat area, subcutaneous fat area, total muscle area, skeletal muscle density	48	86	Sarcopenia can improve predictions of overall survival	[94]
Ferini et al./Italy/2021	Prospective Study	28	Bladder Cancer	Radiotherapy	735	Skeletal muscle index	NA	28.6	Sarcopenia cannot be considered a negative prognostic factor for elderly patients treated with external beam radiotherapy	[141]
Zhang et al./China/2016	Prospective study	113	NA	Chemo-radiotherapy	NA	Total lumbar skeletal muscle cross-sectional area , total lumbar adipose tissue area	NA	84.9	Incidence of sarcopenia among patients with cancer is high, particularly for males	[142]

NA — non-available

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Table 4. Summary of clinical cohort studies regarding the potential impact of cancer immunotherapy and sarcopenia

Author/ Country/ /Year	Study Design	Sample Size	Cancer Type	Immunotherapy	Duration (pre-post therapy in Days)	Body Composition Marker	Rate of Sarcopenia Evaluation		Main Outcomes	Ref.
							Baseline Sarcopenia (%)	Post-therapy sarcopenia (%)		
Non-small Cell Lung cancer (NSCLC)										
Revel et al./ France/2018	Prospective study	779	Lung cancer	Anti-PD-1 Antibody	60	Total muscle area, skeletal muscle index	NA	70	Sarcopenia is associated with higher risk of immunotherapy interruption	[113]
Cortellini et al./ Italy/2019	Retrospective observational study	23	NSCLC	Nivolumab	NA	skeletal muscle index	NA	NA	Influence of nutritional status and sarcopenia on immune response, suggesting these factors could affect treatment with nivolumab	[118]
Nishioka et al./ Japan/2019	Retrospective study	38	NSCLC	Pembrolizumab, nivolumab	NA	Psoas major muscle area	NA	NA	Patients with sarcopenia are associated with poor outcomes for immunotherapy	[110]
Shiroyama et al./Japan/2019	Retrospective study	42	NSCLC	Pembrolizumab, nivolumab	NA	Psoas muscle index	NA	52.4	Sarcopenia at baseline is a significant predictor of worse outcome	[119]
Magri et al./ Italy/2019	Retrospective study	46	NSCLC	Nivolumab	720	Body mass index, skeletal muscle mass index, fat-free mass index, fat mass index, weight change	NA	NA	Weight loss is significant negative prognostic factors for NSCLC patients on immunotherapy	[143]
Popinat et al./ France/2019	Retrospective study	55	NSCLC	Nivolumab	365	Lean body mass, fat body mass, muscle body mass, visceral fat mass, sub-cutaneous fat mass	NA	NA	Subcutaneous fat mass is a significant prognosis factor of stage IV NSCLC treated by nivolumab	[144]

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Table 4 cont. Summary of clinical cohort studies regarding the potential impact of cancer immunotherapy and sarcopenia

Author/ Country/ /Year	Study Design	Sample Size	Cancer Type	Immunotherapy	Duration (pre-post therapy in Days)	Body Composition Marker	Rate of Sarcopenia Evaluation		Main Outcomes	Ref.
							Baseline Sarcopenia (%)	Post-therapy sarcopenia (%)		
Cortellini et al./ Italy/2020	Retrospective study	100	NSCLC, Melanoma, Renal cell carcinoma, others	Pembrolizumab, nivolumab, atezolizumab, others	NA	Hounsfield Unit, skeletal mass index	51	NA	Low skeletal muscle index is associated with shortened survival in advanced cancer patients treated with PD1/PDL1 checkpoint inhibitors	[145]
Roch et al./ France/2020	Retrospective study	142	NSCLC	Pembrolizumab, nivolumab	165	Skeletal mass index	65.7	75.4	Cachexia — sarcopenia syndrome negatively influences patients' outcome during pembrolizumab, nivolumab therapy	[146]
Petrova et al./ Bulgaria/2020	Retrospective study	167	NSCLC	Pembrolizumab	NA	Psoas major muscle area	30.3	NA	Presence of sarcopenia are potential risk factors for the development of disease progression	[147]
Ichihara et al./ Japan/2020	Retrospective study	513	NSCLC	Pembrolizumab, nivolumab, , atezolizumab	NA	Body mass index	NA	NA	BMI was significantly associated with the efficacy of immune checkpoint inhibitors	[148]
Minami et al. Japan/2020	Retrospective study	74	NSCLC	Pembrolizumab, nivolumab, , atezolizumab	NA	Psoas muscle index, intramuscular adipose tissue content, visceral-to-subcutaneous ratio, visceral fat area	NA	NA	Neither sarcopenia nor visceral adiposity may be associated with the efficacy of immune checkpoint inhibitors therapy	[149]
Katayama et al./ Japan/2020	Retrospective study	35	NSCLC	Pembrolizumab, nivolumab, , atezolizumab	NA	Body mass index	NA	NA	Low BMI may be negative predictors for checkpoint inhibitors rechallenge treatment	[150]

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Table 4 cont. Summary of clinical cohort studies regarding the potential impact of cancer immunotherapy and sarcopenia

Author/ Country/ /Year	Study Design	Sample Size	Cancer Type	Immunotherapy	Duration (pre-post therapy in Days)	Body Composition Marker	Rate of Sarcopenia Evaluation		Main Outcomes	Ref.
							Baseline Sarcopenia (%)	Post-therapy sarcopenia (%)		
Tsukagoshi et al./Japan/2020	Retrospective study	30	NSCLC	Nivolumab	NA	Skeletal mass index	NA	NA	Skeletal muscle loss may be a predictive factor of poor outcomes in NSCLS patients undergoing nivolumab therapy	[151]
Takada et al./ Japan/2020	Retrospective study	103	NSCLC	Pembrolizumab, nivolumab	605	Skeletal mass index	NA	NA	L3 muscle index Low is an independent predictor of worse outcomes in NSCLC patients treated with anti-PD-1 inhibitors	[152]
Kichenadasse et al./Australia/2020	Pooled post hoc analysis	1434	NSCLC	Atezolizumab	210	Body mass index	NA	NA	Baseline BMI should be considered as a stratification factor in future immune checkpoint inhibitor therapy trials	[153]
Gastrointestinal										
Kano et al./Japan/2021	Retrospective study	31	Gastric cancer	Nivolumab	NA	Psoas muscle mass index	NA	29	Psoas muscle mass index might help predict the response to nivolumab	[120]
Kim et al./Korea/2021	Retrospective study	149	Gastric cancer	Pembrolizumab, nivolumab	NA	Skeletal mass index	NA	53	Sarcopenia is an independent prognostic factor for progression-free survival in patients treated with PD-1 inhibitors	[154]
Qayyum et al./ USA/2021	Retrospective study	36	Hepatocellular carcinoma (HCC)	Pembrolizumab or nivolumab ± ipilimumab)/ sorafenib	180	Skeletal mass index	NA	NA	Sarcopenia was associated with reduced survival and HCC necrosis	[155]
Akce et al./ USA/2021	Retrospective study	57	Hepatocellular carcinoma	Anti-PD-1 Antibody	180	Skeletal mass index	NA	49.1	Sex-specific sarcopenia does not predict overall survival	[156]

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Table 4 cont. Summary of clinical cohort studies regarding the potential impact of cancer immunotherapy and sarcopenia

Author/ Country/ /Year	Study Design	Sample Size	Cancer Type	Immunotherapy	Duration (pre-post therapy in Days)	Body Composition Marker	Rate of Sarcopenia Evaluation		Main Outcomes	Ref.
							Baseline Sarcopenia (%)	Post-therapy sarcopenia (%)		
Melanoma										
Daly et al./Ireland/2017	Retrospective study	84	Metastatic melanoma	Ipilimumab	100	Muscle attenuation	17	32	Patients with sarcopenia and low muscle index are more likely to experience severe treatment-related toxicity. Loss of muscle during treatment was predictive of worse survival	[112]
Heidelberger et al./France/2016	Retrospective study	71	Melanoma	Pembrolizumab, nivolumab	NA	Body mass index	NA	NA	Patients with sarcopenia experienced significantly more early severe toxicities	[114]
Heidelberger et al./France/2017	Monocentric, retrospective study	68	Melanoma	Pembrolizumab, nivolumab	NA	Body mass index, skeletal muscle index	NA	19	Sarcopenic overweight is associated with more early acute limiting toxicity of anti-PD1 in melanoma patients	[111]
Hu et al./ USA/2020	Retrospective chart review	156	Melanoma	Pembrolizumab	165	Psoas muscle index	NA	34	Sarcopenia did not appear to predict clinically relevant outcomes. Obesity, however, represents a readily available predictor of pembrolizumab toxicity	[157]
Urothelial carcinoma (UC)										
Shimizu et al./ Japan/2020	Retrospective study	27	UC	Pembrolizumab	360	Psoas major muscle area	NA	56	Evaluation of sarcopenia may help in the management of UC with pembrolizumab	[158]
Fukushima et al./Japan/2020	Retrospective study	28	UC	Pembrolizumab	NA	Skeletal muscle index	NA	68	Patients with advanced UC who received pembrolizumab had sarcopenia, which was significantly associated with poor therapeutic efficacy	[159]

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Table 4 cont. Summary of clinical cohort studies regarding the potential impact of cancer immunotherapy and sarcopenia

Author/ Country/ /Year	Study Design	Sample Size	Cancer Type	Immunotherapy	Duration (pre-post therapy in Days)	Body Composition Marker	Rate of Sarcopenia Evaluation		Main Outcomes	Ref.
							Baseline Sarcopenia (%)	Post-therapy sarcopenia (%)		
Others										
Massicotte et al./France/2013	International, double-blinded, placebo-controlled, phase III trial	23	medullary thyroid carcinoma	Vandetanib	90	Visceral adipose tissue, skeletal muscle index	NA	NA	Patients with low muscle mass had high vandetanib serum concentration and high incidence of toxicities	[115]
Veasey-Rodrigues et al./ USA/2013	Prospective Trial	16	Advanced solid tumors	Temsirolimus	63	Skeletal muscle index	44	56	Patients with higher grade toxicities tended to lose more body fat, suggesting a possible end-organ metabolic effect of temsirolimus	[116]
Gyawali et al./ Japan/2016	Retrospective study	20	Breast/ Pancreatic Cancer	Everolimus/ Temsirolimus	180	Body mass index, subcutaneous adipose tissue, visceral adipose tissue, skeletal muscle tissue	60	75	Long-term use of mTOR inhibitors induces a marked loss of muscle mass	[160]

NA — non-available

was the high-ranked marker among the reviewed studies (63.7%), as following: chemotherapy (44.6%) and equal proportion for chemo-radiotherapy and immunotherapy (27.7%). The present study also showed that lower than half of the reviewed studies revealed a significant increase in the rate of sarcopenia (47%) following all cancer therapies (chemo-radio-and immunotherapy).

The direct toxic effects of chemotherapy on skeletal muscle metabolism and loss of muscle mass were reported in 13.7% of the studies, while studies that reported the impact of sarcopenia on a reduction in chemotherapy dosage or a delay in the administration of chemotherapeutic cycles was 10.8% and 7.8% for the administration of immunotherapy. A total of 11.8% of studies showed lowered overall survival by the coinciding impact of chemotherapy and sarcopenia and 14.7% by the coinciding impact of radiotherapy and sarcopenia (Tab. 1). Moreover, the outcomes of the reviewed studies derived from their findings which showed that 93.1% reported a significant negative correlation and prognosis related to the co-occurrence of sarcopenia and cancer therapy (chemo-radio-and immunotherapy) (Tab. 1).

Discussion

Cancer chemotherapy and sarcopenia

In this study, most of the reviewed studies were about the potential impact of cancer chemotherapy and sarcopenia. Chemotherapy immensely strains the body of malignancy patients, causing a more prominent consumption of energy and thus an expansion on the whole-cell catabolic cycles that, subsequently, sabotage tissue creation [16]. Malignancy is conceivably the most remarkable obsessive condition that advances muscle atrophy, especially in elderly patients. On the other hand, sarcopenia is prevalent in patients with various malignancies and the rate of its occurrence in cancer patients varies between 11–74%. It has been recognized that cancer patients with sarcopenia have a poor prognosis regarding various malignancies, such as lung, stomach, pancreas, and colorectal cancers alongside different complications associated with cancer treatment [17, 18]. In addition, long-term outcomes and overall survival are significantly shorter while death rates are more frequently observed in cancer patients with sarcopenia submitted to oncological therapy [19], as reported in studies by Blauwhoff-Buskermolen et al. [20], Liu et al. [21], Ma et al. [22], Paireder et al. [23], Järvinen et al. [24], Choi et al. [25], Jung et al. [26], Miyamoto et al. [27], Derksen et al. [28], Go et al. [29], Prado et al. [30] and Rutten et al. [31].

There is also a direct toxic effect of chemotherapy on skeletal muscle metabolism and loss of muscle mass. This was reported in studies by Blauwhoff-Buskermolen et al. [20], Awad et al. [32], Yip et al. [33], Daly et al. [34], Guinan et al. [35], Cooper et al. [36], Benjamin et al. [37], Sandini et al. [38], Poterucha et al. [39], Eriksson et al. [40], Nattenmüller et al. [41], Goncalves et al. [42], Zargar et al. [43] and Rimar et al. [44].

During cancer chemotherapy, there is a progressive loss of skeletal muscle mass by 1.4 kg after 9 weeks of chemotherapy. In patients receiving systemic chemotherapy for colorectal cancer, deficiency of ≥ 9 % muscle mass during 3 months was freely prescient of lower survival at 6 months. This might be related to uncontrolled muscle protein catabolism that is exaggerated as the tumour growth progresses [20, 45, 46]. As the amount of stored protein diminishes due to sarcopenia, the metabolism and immunity decline relatively to this, prompting an abatement in antitumor response and an increase in mortality [47].

Other possible contributing factors to aggressive loss of muscle mass secondary to low food intake are nausea, vomiting, diarrhoea, anorexia, and fatigue. This is induced by many chemotherapeutic agents particularly by platinum compounds, such as cisplatin, carboplatin, and oxipaltin [48], as also reported by the findings of the present study where platinum-based compounds represented the most common chemotherapeutic agents administered among the reviewed studies within the scope of chemotherapy and sarcopenia. Neuropathy and myalgia secondary to complications by taxanes chemotherapy might induce sarcopenia and skeletal muscle loss [49]. Moreover, cancer chemotherapy may also induce oxidative stress in skeletal muscle tissues through increase production of reactive oxygen species [50, 51], causing a reduction in muscle microvasculature through antiangiogenesis [52] and increase muscle catabolism secondary to the overproduction of tumour growth factors [50, 53].

Lower content of muscular fibres alongside a concomitant decrease of some metabolizing enzymes available in the skeletal muscle tissue could decrease the capability to metabolize some chemotherapeutic agents. An example of these enzymes is dihydropyrimidine dehydrogenase (DPD), which plays an important role in the catabolism of 5-Fluorouracil and capecitabine by converting fluoropyrimidines to inactive metabolites. On the other hand, patients with low lean body mass have poor tolerability and show more toxic adverse effects from anticancer drugs. This is related to a decreased volume of distribution of these agents which may lower the capacity for metabolizing anticancer [54]. Such patients are more prone to a reduction in chemotherapy dosage or a delay in the administration of chemotherapeutic cycles, as reported in studies by Ali et al. [54], Palmela et al. [55], Prado et al. [56], Barret et al. [57], Jung et al. [26], Kurk et al. [58], Go et al. [29], Prado et al. [30], Prado et al. [59], Mazzuca et al. [60], and Zargar et al. [43].

Skeletal muscle mass also decreases during neoadjuvant chemotherapy which might impair the prognosis for adjuvant therapy. Accordingly, maintaining muscle mass during chemotherapy administration is independently associated with disease stabilization and mortality reduction [21, 22, 61].

Literature reported that several molecular pathways have been recognized for muscle protein degradation and skeletal muscle depletion after cancer chemotherapy administration, such as dysregulation in energy metabolism, mitochondrion biogenesis, and dysregulation in muscle fibre metabolism following mitochondrial damage and reduced cytochrome C synthesis needed for oxidative phosphorylation and peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α) [26]. Mammalian Target Of Rapamycin (mTOR) inhibitors, such as everolimus and temsirolimus, involved insulin-like growth factor 1/ /phosphatidylinositol-3-kinase/PKB–protein kinase B)/ /mammalian target of rapamycin pathway in activating skeletal muscle synthesis [62].

Platinum compounds induced sarcopenia to include several pathways, such as ubiquitin-proteasome pathway (UPP) in the degradation of myofibrillar proteins; the autophagy-lysosome pathway (ALP) in the elimination of mitochondria, over-expression of pro-inflammatory cytokines (TNF-α) leading to the activation of the NF-κB pathway, activation of the myostatin pathway, phosphorylation of SMAD2, silences the IGF- 1/PI3K/Akt/mTOR anabolic pathway through the decreased phosphorylation of Akt and mTOR [63]. Doxorubicin and etoposide cause skeletal muscle depletion and muscle protein degradation and direct muscle loss through the activation of the NF-κB molecular pathway. This leads to up-regulation of ubiquitin and proteasomes, increasing the process of proteolysis and production of inflammatory cytokines (IL-1β, IL-6, and TNF-α) which in turn increase E3 ligases (atrogin-1), and the ubiquitin-protein binding for proteolysis [64–66].

Cancer radiotherapy and sarcopenia

Radiation restrains recovery and muscle hypertrophy by harming satellite cells. Radiation is thought to forestall satellite cell mitosis by causing breaks in strands of the cell's DNA. If a break happens just on a single strand, the harm can be fixed by polymerases utilizing the correlative strand as a layout. If harm happens at a similar point on the two strands, the deletion may be irreparable which can prompt mitotic failure and cell death [67].

It has been reported that muscle damage and fibrosis are common and irreversible late effects of radiation on skeletal muscle tissue [68]. Radiotherapy is associated with a wide range of toxic effects that could further deteriorate the nutritional status of cancer patients, such as xerostomia, dysphagia, oral mucositis, oral pain, and sticky saliva [69–71]. Simultaneous chemotherapy and radiation are related to significant toxicities including mucositis, dysphagia, odynophagia, nausea, vomiting, anorexia, fatigue, and dysgeusia bringing about eating difficulty [72–74]. Lower content of muscular fibres, mass and strength are more likely to require radiation treatment breaks and suffer chemotherapy toxicity. These findings were reported in studies by Ganju et al. [73], Li et al. [75] and Panje et al. [76].

Moreover, numerous patients present with symptomatic tumours that lead to eating difficulty preceding the inception of treatment. Patients with HNC going through concurrent chemo-radiotherapy are regularly losing more than 5 % of their body weight in the 6 months around this therapy [77, 78]. To some extent, this has been exacerbated by a change in resting energy consumption, which assists the loss of lean body mass seen during and following treatment. Accordingly, malnutrition might be present nearly in 35-60%, weight loss in 10%, and sarcopenia in up to 70% among patients undergoing radiotherapy for HNC. Therefore, sarcopenia is associated with poor overall and disease-free survival [79], as presented in studies by Cho et al. [80], Mallet et al. [81], van Rijn-Dekker et al. [82], Thureau et al. [83], Sanders et al. [84], Shen et al. [85], Olson et al. [86], Ma et al. [87], Yoon et al. [88], Liang et al. [89], Lee et al. [90], Lin et al. [91], Park et al. [92], Kiyotoki et al. [93], and Pielkenrood et al. [94].

This expanded radiation-induced toxicity in sarcopenic patients contrarily impacts their quality of life since dysphagia altogether impacts the quality of life [95]. Furthermore, an earlier literature review showed that sarcopenia itself was related to an undeniable decrease in quality of life [96]. A recent study reported that sarcopenia is a powerful independent prognostic factor, related to an ascent of the general mortality in patients treated solely by radio-chemotherapy for locally advanced oesophageal cancer. Along these lines, the quality of life in this patient population may be influenced by both radiation-induced toxicities and sarcopenia [81].

Cancer immunotherapy and sarcopenia

The advancement of immune senescence with age is likely a result of many associating cytokine and hormonal adjustments. Increased age, muscle loss, and immune senescence are believed to be interlinked. Skeletal muscle is known to modulate the immune system by producing cytokines (myokines) such as interleukin (IL)-15 and IL-6, and it has been proposed that sarcopenia causes a change in cytokine signalling which modifies immune cells to induce immune dysregulation and

create pro-inflammatory conditions [97–99]. Changes in other immune cell populations, such as expanded myeloid-derived suppressor cells (MDSCs), that have been accounted for with increasing age may likewise be connected to skeletal muscle loss through changes production of myokines [100, 101]. Chronic inflammation within malignancy also adds to sarcopenia. For instance, a high serum level of IL-6, a pro-inflammatory cytokine adding to muscle catabolism, following PD-1 blockade was related to poor response [102, 103]. Therefore, combined blockade of IL-6 and PD-1/PD-L1 signalling exerts synergistic anti-tumour effects [104]. Furthermore, restricting T cell infiltration in the tumour due to transforming factor-β signalling, an immunosuppressive cytokine that additionally adds to sarcopenia [105, 106]. On the other hand, peroxisome proliferator-initiated receptor-gamma coactivator (PGC)-1α is a key factor created in the muscle that has fundamental negative impacts on the anti-tumour immune response. Along these lines, skeletal muscle loss may prompt expanded creation of TGF-β and IL-6, and diminished creation of PGC-1α and other myokines [107, 108], which might be related to poor response to PD-L1 blockade. Hence, sarcopenia has been related to poor outcomes or toxicity to tyrosine kinase inhibition, and to immune checkpoint inhibitors (ICIs), including programmed cells death 1 (PD-1) inhibitors, such as nivolumab and pembrolizumab [109, 110]. This was evidenced in earlier studies by Heidelberger et al. [111], Daly et al. [112], Revel et al. [113], Heidelberger et al. [114], Massicotte et al. [115], and Veasey-Rodrigues et al. [116].

Sorafenib through multiple steps causes inhibition of PI3K, Akt, and mTOR which are directly involved in the activation of amino acid transporters and synthesis of muscle protein alongside inhibition of the physiologically activated pathways following the physical exercise involving RAF, MEK, and MAPK/ERK kinase. Moreover, it causes a reduction in muscle blood supply and substrates delivery to the muscle through antiangiogenesis properties [117]. The PD-1 inhibitors, such as nivolumab or pembrolizumab, block the PD-1/programmed death-ligand 1 (PD-L1) pathway by which malignancy cells escape immune recognition. Sarcopenic patients treated with nivolumab for non-small cell lung carcinoma (NSCLC) had more limited progression-free survival and overall survival [118]. Moreover, earlier studies found a significant relationship between sarcopenia, shorter progression-free survival, and lower response rate in NSCLC patients treated with PD-1 checkpoint inhibitors [110, 119]. A higher incidence of adverse events was also reported in sarcopenic melanoma patients treated with PD-1 inhibitors [111, 120] and ipilimumab [112].

Conclusion

Despite the high proportion of the reviewed studies that were retrospectively conducted, it was observed that the dual impact from coinciding potential complications of cancer therapy and sarcopenia are highlighted. Consequently, the evaluation of sarcopenia in cancer patients should be considered as a primary part of oncology care in cancer patients receiving diverse lines of cancer therapy.

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The authors declare that there is no conflict of interest.

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Consent to participate

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